

### Remarks

Claims 1-3, 7, 9-10 and 12-13 have been rejected under 35 U.S.C. 112 first paragraph for lack of enablement. The rejection is based upon the allegation that enablement is not provided for providing a secondary immune response to non-enteric pathogen antigens (NEPA's). This position by the Examiner is refuted, especially as it applies to the NEPA's selected from the group consisting of hepatitis C, hepatitis delta, yellow fever, dengue hemorrhagic fever, tetanus, staphylococcus aureous, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever as set forth in claim 3.

The rejection should be withdrawn since there is in fact clear enabling support in the specification, especially when considered in conjunction with the knowledge of one skilled in the art.

In making this rejection, the Examiner has said "The specification does not disclose other specific non-enteric pathogen antigens which have been subjected to the claim designated therapeutic regimen, nor does the specification teach any methodology associated with the making of genetically altered plant materials expressing any other NEPA other than the non-enteric pathogen antigen, hepatitis B surface antigen."

The Examiner's statement is insufficient to support the rejection. Enablement is not solely dependent upon the precise words of the specification, but must also include the knowledge of one skilled in the art. One skilled in the art clearly knows how to make the required genetically altered plant materials and in the 35 U.S.C. 103 rejections discussed infra, the Examiner has relied upon cited patents that clearly teach how to make the required plant

materials and patents cited by the Examiner in fact have generically claimed such plant materials. This issue of enablement has thus already been decided by the U.S.P.T.O. For example, in the 35 U.S.C. 103 rejection, the Examiner has relied upon U.S. Patent 6,136,320 to Arntzen et al. Claim 1 of that patent says:

“An orally acceptable immunogenic composition comprising unpurified or partially purified recombinant viral immunogen expressed in a plant, wherein said immunogen is expressed in the plant at a level such that upon oral administration of said composition to an animal, an immunogenic response is observed.”

Allowance of this claim clearly shows that the patent office has at least once accepted the fact that one skilled in the art now knows how to cause a plant to express a viral immunogen (antigen). If the Examiner were to maintain that one skilled in the art were not enabled to cause a plant to express an immunogenic viral antigen, he would, in essence, be taking a position that the patent he is relying upon contains an unsupported teaching and improperly supported claims. From a breadth perspective, the present application claims the same thing as U.S. Patent 6,136,320, except that in the presently claimed invention, it has been unexpectedly discovered that immunogens from non-enteric pathogens can be included that do not raise an oral primary immune response but can be used to obtain a secondary oral immunogenic response, if the animal is first vaccinated (non-orally). The teachings in the specification are more than adequate to support this additional step for any viral immunogen within the previously accepted disclosure and claims of U.S. Patent 6,136,320.

The Examiner’s attention is also drawn to U.S. Patent 5,679,880 in which claim 1 says:

“A transgenic plant, comprising and expressing a DNA sequence coding for an antigen of a pathogenic microorganism or an antigenic determinant thereof, said antigen or antigenic determinant thereof eliciting a secretory immune response in a human or other animal upon oral administration of tissue of said plant.”

Similar disclosures and claims deemed supported by the U.S.P.T.O. are given in U.S. Patents 5,686,079 and 5,654,184.

Again it is clear that the U.S.P.T.O. has already decided that there is enablement for the base issues raised by the Examiner, i.e. one skilled in the art knows how to make plants and plant material expressing antigens from pathogenic microorganisms and further knows that they can be orally administered to obtain an immune response when the antigen is capable of eliciting such a response. The improvement in accordance with the present invention is that it has now been discovered that NEPA's which are otherwise not capable of eliciting any meaningful primary immune response orally, can be made to orally elicit a secondary immune response when the animal in question is previously vaccinated or immunized against the NEPA non-orally. This improvement is not obvious from the cited art but is clearly enabled by the teachings of the present specification in conjunction with the known state of the art.

Claims 1-3, 7, 9-10, and 12-13 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite.

This rejection should be withdrawn.

The objections to Claim 1, lines 2 and 3 have been obviated by amendment.

The objection to Claim 1, lines 5-6 should be withdrawn. Any person skilled in the art knows what vaccination by injection means. Further, it does not matter whether the vaccination is by a whole virus containing an NEPA or an isolated NEPA, so long as an immune response to the NEPA results. One skilled in art clearly knows this also.

The generic objection with respect to grammatical and idiomatic errors cannot be addressed. The generic objection is not understood. To the knowledge of the Attorney for the Applicants, the claims in fact do conform to U.S. practice and are not indefinite. The Examiner's reference to "narrative" is not understood. The claims are in the form of descriptive sentences as required. Further, to the knowledge of the Attorney for the Applicants, there are no grammatical or idiomatic errors and the Examiner has pointed to none. The objection is therefore improper and should be withdrawn.

The attorney for the applicants appreciates the Examiner's pointing out the spelling error in claim 3. The error has been corrected by amendment.

Claims 1-3, 7, 9-10, and 12-13 have been rejected under 35 U.S.C. 103 as being unpatentable over Arntzen et al. (A, U.S. Patent 5,914,123) or Arntzen et al. (B, U.S. Patent 6,136,320 in view of Stites (U) and further in view of readily admitted prior art.

The rejection is improper and should be withdrawn.

It is admitted that cited art discloses administration of immunogens expressed in plants to obtain an immune response; however, there is no suggestion of first administering the immunogen by injection and secondly administering the immunogen orally to obtain an oral response not otherwise obtainable. None of the cited art in any combination suggests such a

method. Such a concept is not obvious in view of the cited art. **Prior to the present invention, initial injection of an NEPA (alone or in a more complex viral package) followed by oral administration of the NEPA to obtain an immune response was never suggested and never tried.** Until the present invention, no person skilled in the art would have recognized that an oral response to an NEPA, that does not normally yield an oral response, could be obtained by first obtaining a non-oral response, e.g. by injection.

The rejection is therefore clearly improper and should be withdrawn.

Arntzen et al. teaches a method for making a transgenic tobacco, tomato or potato that expresses HBsAg.

Notwithstanding the Examiner's assertion, **Arntzen et al. references do not teach "methods of making a transgenic plant expressing an immunogen derived from hepatitis B surface antigen, wherein the immunogen is capable of eliciting an immune response in an animal by consumption of the plant material."**

Arntzen et al. "A" itself teaches and recognize that not all antigens would cause an immune response if ingested **and there is no suggestion as to how to make NEPA's raise an oral immune response. Until the present invention, it was simply not obvious.**

Arntzen et al. "A" says in column 15 beginning at line 27,  
"The vaccines are conventionally administered parentally, by injection, for example either subcutaneously or intramuscularly. Additional formulations which are suitable for other modes of administration include suppositories and, *in some cases*, oral formulations or aerosols." (emphasis added).

But there is no teaching or suggestion in either Arntzen et al. reference of how the "some cases" could be determined or how the "some cases" could be accomplished.

While Arntzen et al. "A" suggests that tomato juice containing HBsAg **might** be used as a vaccine, in fact Arntzen provides no supporting data showing any oral immune response whatsoever to tomato juice or any other plant containing HBsAg. To the extent that the Arntzen et al. references teach that tomato juice or any other plant material containing HBsAg can be used as an oral vaccine, they are inoperative references, since there is no teaching or suggestion as to how that might be done. *Simply ingesting the plant material, as suggested by Arntzen et al., does not confer immunity.*

There is good reason for Arntzen's omission of data showing immune response to HBsAg by ingesting food material containing it, since prior to the present invention, in fact, there was little if any immune response whatsoever to HBsAg in orally ingested tomato juice or any other plant expressing HBsAg. See the **Rule 132 Declaration of Dr. Thanavala** of record. The response, if any, is clearly insufficient for that purpose.

Reference to the examples in the present specification clearly illustrates that priming of the subject of the immunization is required by either pre-vaccination or the use of an effective adjuvant. The Arntzen et al. references suggests neither. **The Arntzen et al. references simply do not suggest preimmunization by injection followed by oral feeding of a transgenic potato expressing a NEPA to obtain a secondary immune response as required by the present claims.**

Arntzen's suggestion of simple ingestion of plant material expressing HBsAg does not give a sufficient immune response to be considered protective. Arntzen discloses or suggests no

way in which a high immune response could be orally obtained and the other cited references do not remedy that critical defect as previously discussed.

Simply making an unsupported allegation in a reference without a teaching as to how the allegation might be accomplished, is not a sufficient teaching to make a method for accomplishing the desired result obvious to one skilled in the art. Prophetic statements cannot be used to form the basis of a rejection, especially when they are unsupported and not true.

The Arntzen et al. B reference 6,136,320 pays lip service to raising an immune response by ingestion, but in fact give no examples or teachings for obtaining such a result. **The only actual plant examples in Arntzen et al. relate to tomatoes and tobacco. There is no example of ingestion of either one raises an immune response.** In fact, ingestion of the transgenic tomato does not raise any significant immune response (see the Rule 132 Declaration of Dr. Yasmin Thanavala of record) and certainly tobacco cannot be used for such a purpose because it is toxic. **There is simply no teaching in either of the Arntzen et al. references of how oral immunization to any NEPA could be accomplished using a transgenic plant, and in fact the plants made in the examples do not function orally to raise an immune response to any NEPA.** Arntzen certainly does not suggest that a potato expressing a NEPA could raise a secondary immune response when fed subsequent to immunization by injection, as presently claimed. **It is therefore clear that there is insufficient teaching or suggestion in the Arntzen et al. references to support a rejection of the present claims whether or not the references are considered alone or in combination with Stites.**

Stites et al. adds nothing to cure the inadequate teachings and suggestions of the Arntzen et al. references. Stites et al. does not suggest anything concerning orally raising an immune response to an antigen expressed by a plant. Further, Stites et al. clearly does not suggest any method for **orally** raising a highly effective secondary immune response by feeding a potato expressing an antigen after prior injection of the antigen.

In view of the foregoing amendments and remarks, it is therefore courteously requested that all rejections be withdrawn and all claims be allowed.

Respectfully submitted,



Michael L. Dunn

Attorney for Applicant(s)

Reg. No. 25,330

P.O.Box 96

Newfane, New York 14108

Telephone: (716) 433-1661

MLD/cah

cc: M. DeLellis

## Version with markings to show changes made

### In the claims

Claim 1 has been amended as follows:

1. (thrice amended) A method for providing a secondary immune response in a mammal to a specific antigen [to] of a non-enteric pathogen (NEPA) , the pathogen being a pathogen that invades through a breach in the skin and that does not itself enterically raise a primary protective [enteric] immune response in mammals [free] in the absence of prior acquired immunity to the pathogen, said method comprising: rendering the mammal immunoreceptive to the NEPA by prior immunization against a non-enteric pathogen containing the NEPA by vaccination by injection; and then [followed by oral] orally administering the NEPA to the [administration by feeding the] immunoreceptive mammal by feeding the mammal with transgenic potato containing the NEPA expressed in the potato to enterically cause a secondary immune response to the oral administration specific to the NEPA stronger than would be caused by orally administering [a response specific to NEPA caused by] the NEPA in the absence of the prior immunization by injection.

Claim 3 has been amended as follows:

3. (thrice amended) The method of Claim 2 wherein the NEPA is an antigen specific to a non-enteric pathogen selected from the group consisting of those that cause hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue [hemoragic] hemorrhagic fever, tetanus, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever.